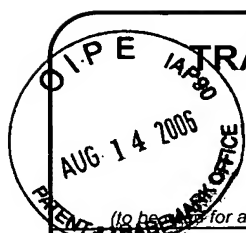
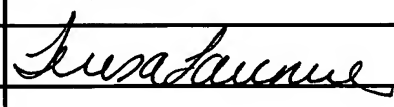


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 <b>TRANSMITTAL FORM</b> (to be used for all correspondence after initial filing)	Application Number	10/724,638
	Filing Date	December 2, 2003
	First Named Inventor	Gautam Vinod Daftary et al.
	Art Unit	1623
	Examiner Name	Leigh C. Maier
Total Number of Pages in This Submission	Attorney Docket Number	12879/3

ENCLOSURES (check all that apply)		
<input type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment / Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input checked="" type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Reply to Missing Parts/Incomplete Application <input type="checkbox"/> Reply to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ <input type="checkbox"/> Landscape Table on CD	<input type="checkbox"/> After Allowance Communication to TC <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input type="checkbox"/> Other Enclosure(s) (please identify below):
<div style="border: 1px solid black; padding: 5px;"> <b>Remarks</b>    </div>		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm	Customer No. 23838		
Signature			
Printed Name	Teresa A. Lavenue		
Date	August 14, 2006	Reg. No.	47737

CERTIFICATE OF TRANSMISSION/MAILING			
I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.			
Signature			
Typed or printed name		Date	

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Attorney Docket No. 12879/3

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Confirmation No.: 2014

INVENTORS : Gautam Vinod Daftary et al.  
APPLICATION NO. : 10/724,638  
FILED : December 2, 2003  
FOR : AQUEOUS IFOSFAMIDE COMPOSITIONS FOR  
PARENTERAL ADMINISTRATION AND A  
PROCESS FOR THEIR PREPARATION  
EXAMINER : Leigh C. Maier  
ART GROUP : 1623

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**SUBMISSION OF PRIORITY DOCUMENT**

Sir or Madame:

Submitted herewith is a certified copy of the priority document for the above-identified application.

Respectfully submitted,  
KENYON & KENYON LLP

Teresa A. Lavenue  
Reg. No: 47,737

Date: August 14, 2006

1500 K Street, N.W.  
Washington, D.C. 20005  
Telephone: (202) 220-4258  
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Customer 23838

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**CERTIFIED COPY OF  
PRIORITY DOCUMENT**

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FORM 1

*THE PATENTS ACT, 1970 (39 of 1970)*  
*APPLICATION FOR GRANT OF A PATENT*  
*[See sections 5(2), 7]*

1. We, **Bharat serums & Vaccines Ltd., Road No. 27, Wagle Estate, Thane - 400 604. Maharashtra, India.**  
an Indian company incorporated under the Companies Act 1956,
2. hereby declare
  - a) that we are in possession of an invention titled "A process for the manufacture of low toxicity, stable Ifosfamide parenteral solution."
  - b) that the **provisional specification** relating to this invention is filed with this application.
  - c) that there is no lawful ground of objection to the grant of a patent to us.

3. We further declare that the inventors for the said invention are
  - a) **Dr. Daftary Gautam Vinod**  
**Bharat Serums & Vaccines Ltd., Road No. 27, Wagle Estate**  
**Thane - 400 604., Maharashtra, India**  
**Nationality - Indian**

b) **Mr. Pai Srikanth Annappa**  
**Bharat Serums & Vaccines Ltd., Road No. 27, Wagle Estate**  
**Thane - 400 604., Maharashtra, India**  
**Nationality - Indian**

c) **Ms. Rivankar Sangeeta Hanurmeh**  
**Bharat Serums & Vaccines Ltd., Road No. 27, Wagle Estate**  
**Thane - 400 604., Maharashtra, India.**  
**Nationality - Indian**

The application  
is Post dated to  
02.12.2002 u/s.

17(1) of the P.A.  
1970.

(D.P. Patil)

Exm of Effect &  
Design.

We claim the priority from the application filed in convention countries, particulars of which are as follows - **None**

5. We state that the said invention is an improvement in or modification of -  
**Not Applicable**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application be deemed to have been filed on \_\_\_\_\_ under section 16 of the Act. - **Not Applicable**

7. That we are the assignee or legal representative of the true and first inventor.

D. P. Patil  
7.5.1.2001  
29.8.2002



8. That our address for service in India is as follows :

**Srikanth Pai**  
**Bharat Serums & Vaccines Ltd., Road No. 27, Wagle Estate**  
**Thane - 400 604., Maharashtra, India**

9. Following declaration was given by the inventors.

We, the true and first inventors for this invention declare that the applicant herein is our assignee.

- a) ..... **DR. DAFTARY GAUTAM VINOD** Dt.
- b) ..... **PAI SRIKANTH ANNAPPA** Dt.
- c) ..... **RIVANKAR SANGEETA HANURMESH** Dt.

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachments with the application.
- a) Provisional specification - 3 copies
  - b) Fee Rs. 5,000.
  - c) Statement and undertaking on Form 3.

We request that a patent may be granted to us for the said invention.

Dated this 21<sup>st</sup> day of August 2002.

For **BHARAT SERUMS & VACCINES LTD.**

*[Signature]*  
**DR. DAFTARY GAUTAM VINOD**  
Director

To  
The Controller of Patents  
The Patent Office  
Mumbai.

**FORM 2**

*THE PATENTS ACT, 1970  
PROVISIONAL SPECIFICATION  
[See section 10]*

**DUPLICATE**

*Title*

***"A process for the manufacture of  
low toxicity, stable Ifosfamide  
parenteral solution"***

*Applicant*

***BHARAT SERUMS & VACCINES LTD.,  
Road No. 27, Wagle Estate,  
Thane - 400 604. Maharashtra, India.***

*an Indian company incorporated under the Companies Act 1956,*

The following specification describes the nature of the invention

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MUM  
29 AUG 2002

This invention relates to a process for preparation of a low toxicity, stable compositions for parenteral administration containing Ifosfamide. This invention is particularly related to a process for preparation of Ifosfamide compositions in which Ifosfamide is complexed with 2-hydroxypropyl- $\beta$ -cyclodextrin (referred to hereinafter as "HPBCD"). This invention is more particularly related to a process of preparation of a clear aqueous composition of Ifosfamide HPBCD complex having low toxicity and that is stable over a period of time that makes it suitable for ready clinical use.

***Background and prior art :***

Two main groups of drugs used in the treatment of malignant disease are Alkalyting agents and the antimetabolites. Ifosfamide is one of the widely used antineoplastic drug belonging to the alkalyting agents group. It is used in the treatment of a variety of solid tumors including those of the cervix, endometrium, lung, ovary, testes and thymus as well as in sarcoma and in the treatment of Burkitts lymphoma.

Ifosfamide is given intravenously either by injection as a solution diluted to less than 4% or by infusion.

Ifosfamide is a white crystalline powder having a low melting point of 40°C. The powder is also hygroscopic. Both these characteristics of Ifosfamide make it difficult for sterile filling of the dry powder as both temperature and humidity are required to be accurately controlled. Further, as Ifosfamide powder is filled aseptically into sterile containers, maximum precautions are required to maintain sterility of the product.

Even though Ifosfamide powder is freely soluble in water, the solubility decreases on storage. Ifosfamide has been reported to undergo a reversible chemical rearrangement in aqueous solution, which is sensitive to changes in pH. The ratio of these compounds to one another in biological fluids have a bearing on the toxicity and efficacy of Ifosfamide.

US 4952575 discloses an invention in which Oxazaphosphorin is dissolved in very high concentrations up to 100% of ethanol. Even though the degradation has been shown to be minimal for Ifosfamide, use of solvents in such a high concentration leads to other

problems such as volatility, handling during manufacturing, miscibility with blood. As such alcohol is pharmacologically active which may also affect the person on administration of alcoholic solution of Ifosfamide.

WO 99/18973 discloses an invention in which Ifosfamide in saline solution. The product ~~has been shown to be stable at refrigerated temperatures. The stability data provided does~~ not show satisfactory stability at elevated temperatures.

US 4879286 discloses an invention in which Cyclophosphamide is formulated in a ready-to-dilute solution. This invention uses organic Polyol as a solvent and also 0 to 50% water. The water may be partly replaced by 10 to 30% of ethanol. The ready-to-dilute solutions have been shown to be stable under refrigerated conditions. However, the stability data at elevated temperatures are not sufficient to prove that the product is stable.

Our main objective of this invention is thus to develop a process for preparing low toxicity, stable compositions of Ifosfamide complexed with HPBCD overcoming all the disadvantages of prior arts and make the composition suitable for parenteral administration in human beings and mammals.

Accordingly, the invention relates to a process for preparation of a low toxicity, stable compositions of Ifosfamide suitable for parenteral administration comprising steps of

- i) addition of Ifosfamide as such or in an aqueous solution form to an aqueous solution of HPBCD in a molar ratio of HPBCD : Ifosfamide 1 : 0.4 to 1 : 30;
- ii) mixing the aqueous solution of HPBCD and Ifosfamide to bring intimate contact;
- iii) filtering the composition obtained through 2 $\mu$  and 0.2 $\mu$  filter successively;
- iv) filling aseptically the filtrate obtained at the end of step (iii) in sterile containers such as vials, ampoules, plastic containers followed by nitrogen purging and sealing the filled containers.

The process of present invention further comprises addition of conventional additives as required by parenteral dosage form before filtration step.

The Ifosfamide content of the composition of this process of invention is from about 1mg/ml to about 200mg/ml, preferably from about 10mg/ml to 100mg/ml, more preferably from about 40mg/ml to about 50mg/ml.

The preferred molar ratio of HPBCD to Ifosfamide is from about 1 : 0.4 to 1 : 30. The more preferred molar ratio is from about 1 : 1 to 1 : 5. More preferably from about 1 : 2 to 1 : 3.

The conventional parenteral additives, which may be used in the process of this invention, contain commonly used additives such as buffers, isotonic diluents and anticrystallising agents. These conventional parenteral additives when added in the usual recommended range do not affect the clarity and stability of the composition adversely.

Buffers are selected from a group of pharmaceutically acceptable buffer systems such as Phosphate buffer, Citrate buffer, Glycine buffer containing any of the commonly used compounds or a mixture of compounds such as Citric acid, Sodium citrate, Potassium citrate, Glycine, Phosphoric acid, Sodium phosphate, Disodium hydrogen phosphate, Sodium dihydrogen phosphate, Potassium phosphate, Dipotassium hydrogen phosphate, Potassium dihydrogen phosphate, Sodium hydroxide, Potassium hydroxide, Hydrochloric acid. Preferably the buffer used is a mixture of Sodium dihydrogen phosphate and Disodium hydrogen phosphate.

### **Examples :**

The invention will now be illustrated by way of Examples. The Examples are by way of illustration only and in no way restrict the scope of the invention.

All the raw materials used in this Examples were of parenteral grade. Equipments used were of conventional nature. Entire processing was done in an area with a controlled environment. Nitrogen cover was provided while processing the batch.

### Example I :

1.	Ifosfamide	-	10g
2.	HPBCD	-	20g
3.	Disodium hydrogen phosphate	-	0.1g
4.	Sodium dihydrogen phosphate	-	0.06g
5.	Water	-	q.s. to 200ml

Weighed quantities of Disodium hydrogen phosphate and Sodium dihydrogen phosphate were dissolved in 160ml of water. Weighed quantity of HPBCD was added and dissolved slowly under stirring in this buffer solution. Weighed quantity of Ifosfamide was gradually added under stirring to the buffered HPBCD solution and mixed for 3 hours. The volume was made up to 200ml with water. The product was filtered through 0.2 $\mu$  filter and filled aseptically in sterile glass vials. The glass vials were closed under aseptic conditions with sterile Teflon coated rubber bungs and sealed using flip off seals.

The composition obtained in this Example was analysed for Ifosfamide content by High Pressure Liquid Chromatography (HPLC) method and was found to contain 50.23mg/ml of Ifosfamide. The composition had a pH of 7.2.

### Example II :

The composition obtained in Example I was subjected to acute toxicity studies in mice. Conventional formulation after reconstitution as directed by the manufacturer was used as a control. Both the drug solutions were suitably diluted with 5% Dextrose Injection and administered intravenously. Ifosfamide in the dose range of 500mg/kg, 600mg/kg and 700mg/kg body weight was administered in three different groups of animals, each group consisting of eight animals.

Animals were kept under observation for 14 days. Animals were observed for mortality at the end of 3 days and 7 days.

It was observed that the LD<sub>50</sub> dose i.e. the dose that is lethal to 50% of animals was much higher for composition of Example I in comparison with the Conventional formulation.

Composition of Example I			Conventional formulation		
<i>Dose (mg/kg)</i>	<i>Mortality (%)</i>		<i>Dose (mg/kg)</i>	<i>Mortality (%)</i>	
	3 Days	7 Days		3 Days	7 Days
500	0	0	500	12.5	25
600	0	12.5	600	50	75
700	0	12.5	700	62.5	75

This clearly shows that composition of the invention prepared in Example I is less toxic compared to the Conventional formulation.

#### **Example III :**

The composition obtained in Example I was subjected to Stability studies. Samples were incubated at 2°C - 8°C and also at 25°C. The stability data at the end of 6 months shows insignificant drop in Ifosfamide content at 25°C indicating a good stability.

#### **Example IV :**

- |    |                             |   |               |
|----|-----------------------------|---|---------------|
| 1. | Ifosfamide                  | - | 20g           |
| 2. | HPBCD                       | - | 40g           |
| 3. | Disodium hydrogen phosphate | - | 0.1g          |
| 4. | Sodium dihydrogen phosphate | - | 0.06g         |
| 5. | Water                       | - | q.s. to 200ml |

The composition was prepared using the same procedure as described under Example I.

**Example V :**

- |    |                             |   |               |
|----|-----------------------------|---|---------------|
| 1. | Ifosfamide                  | - | 10g           |
| 2. | HPBCD                       | - | 80g           |
| 3. | Disodium hydrogen phosphate | - | 0.1g          |
| 4. | Sodium dihydrogen phosphate | - | 0.06g         |
| 5. | Water                       | - | q.s. to 200ml |

The composition was prepared using the same procedure as described under Example I.

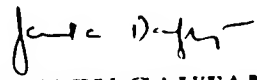
**Example VI :**

- |    |            |   |               |
|----|------------|---|---------------|
| 1. | Ifosfamide | - | 10g           |
| 2. | HPBCD      | - | 20g           |
| 3. | Water      | - | q.s. to 200ml |

The composition was prepared using the same procedure as described under Example I except that HPBCD was dissolved in water in place of buffer solution.

Dated this 21<sup>st</sup> day of August 2002

For **BHARAT SERUMS & VACCINES LTD.**

  
**DR. DAFTARY GAUTAM VINOD**  
Director

To,  
The Controller of Patents  
The Patent Office  
At Mumbai.

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